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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/993,211	11/16/2001	Beryl Asp	01-1720	8080

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EXAMINER
UNGAR, SUSAN NMN

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/01/2005

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/993,211	ASP ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *18 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *2,3,7-12 and 14-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,4-6 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. The Amendment filed November 18, 2004 and the Supplemental Response and executed Declaration filed December 16, 2004 in response to the Office Action of May 18, 2004 are acknowledged and have been entered. 1, 4-6 and 13 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The following rejections are being maintained:

Claim Rejections - 35 USC 112

4. Claims 13 remains rejected under 35 USC 112, first paragraph for the reasons previously set forth in the paper mailed May 18, 2004, Section 8, pages 3-10.

Applicant argues that the specification provides information to enable the full scope of claim 13, that is a method for ameliorating cardiotoxic effects caused by trastuzumab alone which comprises an effective amount of dexrazoxane on pages 4-5 of the specification.

The argument has been considered but has not been found persuasive for the reasons previously set forth.

Applicant argues that Applicant's found that trastuzumab administered alone, contrary to the Examiner's contention, was cardiotoxic based on clinical data and Applicant point to page 2, lines 18-20.

The argument has been considered but has not been found persuasive. A review of page 2 reveals the statement that "an overview of clinical data indicates that the use of trastuzumab is sometimes associated with an undesired cardiotoxicity". The specification does not reveal who reviewed the clinical data, which clinical data was reviewed or whether trastuzumab was used only or in

combination with known cardiotoxic chemotherapeutics. However, it is clear that given the teachings of Cook-Bruns, of record who teaches that Herceptin has no inherent cardiotoxicity and does not directly lead to cardiac failure, given the teachings of Gianni of record who offered numerous hypotheses to explain adverse cardiac events associated with Herceptin clinical trials including observation artifacts and the amplification of anthracycline cardiotoxic effects, given the teachings of Ewer et al, of record, who also offered numerous hypotheses to explain adverse cardiac events associated with trastuzumab toxicity including observational artifacts and sequential stresses following doxorubicin administration, given the teachings of Sparano et al who established that monkeys treated with trastuzumab at doses more than 10-fold higher than in humans for up to 6 months did not have any evidence of cardiac toxicity, no one would believe it more likely than not that any nexus has been established, between trastuzumab adminstration alone and cardiotoxicity, based only on the cited overview of undefined clinical data.

Applicant argues that conditions for administering an effective amount of dexrazoxane to ameliorate cardiotoxic effects caused by trastuzumab when administered alone is described on page 6, which provides a protocol scheme to determine the effectiveness of dexrazoxane and the dose levels to ameliorate cardiotoxicity. The argument has been considered but has not been found persuasive for the reasons of record. The protocol scheme to determine the effectiveness of dexrazoxane is not enabling because the cardiotoxicity of trastuzumab has not been established and even if it were to be established, it is unknown if the mechanism of action of dexrazoxane will be effective to ameliorate the cardiotoxicity for the reasons of record.

Applicant teaches the requirements of 35 USC112 drawn to written description and enablement and argues that Applicants have submitted an enabling disclosure because (a) page 2, line 20 establishes the cardiotoxic effects of trastuzumab, (b) dexrazoxane is a known compound, (c) working examples are not required to show enablement and guidance is provided for dosages of dexrazoxane that will function as claimed and a protocol scheme is provided to determine the effectiveness of dexrazoxane thus the specification provides abundant support and instruction to teach those skilled in the art how to practice the claimed invention, (d) Examiner did not address the breadth of the claims and since the claims are drawn to administering a known compound for ameliorating cardiotoxic effects caused by a known compound, the claims are enabled and there is no difficulty in reducing the invention to practice without undue experimentation, (e) Examiner did not address the relative skill in the art and since the methods of making trastuzumab and dexrazoxane are known in the art, the level of skill in the art is very high.

The arguments have been considered but have not been found persuasive (a') for the reasons set forth previously and above, (b') although dexrazoxane is a known compound it is unknown whether or not it could ameliorate cardiotoxic effects of trastuzumab, if it were to be found that trastuzumab indeed has cardiotoxic effects, for the reasons of record, (c') although working examples are not required, given the teaching of those skilled in the art, for the reasons of record it cannot be determined from the specification as originally filed whether trastuzumab is indeed cytotoxic or whether if cytotoxic, dexrazoxane would be useful to ameliorate the putative cytotoxic effects of trastuzumab, (d') Applicant has admitted on the record that the claimed invention has not been reduced to

practice. Given the teaching of those skilled in the art, for the reasons of record it cannot be determined from the specification as originally filed whether trastuzumab is indeed cytotoxic or whether if cytotoxic dexrazoxane would be useful to ameliorate the putative cytotoxic effects of trastuzumab and it is clear, given that the invention has not been reduced to practice, that undue experimentation would be required to practice the claimed invention, (e') it cannot be determined from the specification as originally filed whether trastuzumab is indeed cytotoxic or whether if cytotoxic dexrazoxane would be useful to ameliorate the putative cytotoxic effects of trastuzumab. The level of skill in the art is not drawn to the instantly claimed invention.

The arguments have been considered but have not been found persuasive and the rejection is maintained.

Claim Rejections - 35 USC 103

5. Claims 1, 4-6 remains rejected under 35 USC 103 for the reasons previously set forth in the paper mailed May 18, 2004, Section 11, pages 10-12.

Applicant argues that the primary reference does not teach the . administration of DZR in combination with herceptin and that Swain does not remedy the deficiencies in the primary reference because Swain does not disclose, suggest or teach the addition of dexrazoxane effective to ameliorate cardiotoxicity associated with Herceptin administration. Neither reference teaches that Herceptin is associated with toxicity.

The argument has been considered but has not been found persuasive because the claims as currently constituted are not limited to dexrazoxane treatment effective to ameliorate cardiotoxicity associated with Herceptin administration since the claims are not limited to the treatment of cancer with

Herceptin alone. The claims are specifically drawn to treatment of cancer **comprising** (emphasis added) administering trastuzumab. The claims as currently constituted clearly read on the treatment of the combined references. Although Swain does not disclose the addition of dexrazoxane to a Herceptin alone protocol, Swain provides both means and motivation to add dexrazoxane to the protocol of the primary reference which comprises both Herceptin and doxorubicin for the reasons of record. Finally, given the information in the art and set forth previously, it is not surprising that neither reference teaches that Herceptin is associated with toxicity. Again, the claims as currently constituted are not limited to treatment of Herceptin cardiotoxicity and the claims are obvious for the reasons of record.

The arguments have been considered but have not been found persuasive and the rejection is maintained.

6. No claims allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at 571-272-0787. The fax phone number for this Art Unit is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Susan Ungar
Primary Patent Examiner
February 24, 2005